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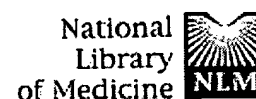
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Synergy between an antiangiogenic integrin alphav antagonist and an antibody-cytokine fusion protein eradicates spontaneous tumor metastases.

Lode HN, Moehler T, Xiang R, Jonczyk A, Gillies SD, Cheresh DA, Reisfeld RA.

The Scripps Research Institute, Department of Immunology, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA.

The suppression and eradication of primary tumors and distant metastases is a major goal of alternative treatment strategies for cancer, such as inhibition of angiogenesis and targeted immunotherapy. We report here a synergy between two novel monotherapies directed against vascular and tumor compartments, respectively, a tumor vasculature-specific antiangiogenic integrin alphav antagonist and tumor-specific antibody-interleukin 2 (IL-2) fusion proteins. Simultaneous and sequential combination of these monotherapies effectively eradicated spontaneous liver metastases in a poorly immunogenic syngeneic model of neuroblastoma. This was in contrast to controls subjected to monotherapies with either an antiangiogenic integrin alphav antagonist or antibody-IL-2 fusion proteins, which were only partially effective at the dose levels applied. Furthermore, simultaneous treatments with the integrin alphav antagonist and tumor-specific antibody-IL-2 fusion proteins induced dramatic primary tumor regressions in three syngeneic murine tumor models, i.e., melanoma, colon carcinoma, and neuroblastoma. However, each agent used as monotherapy induced only a delay in tumor growth. A mechanism for this synergism was suggested because the antitumor response was accompanied by a simultaneous 50% reduction in tumor vessel density and a 5-fold increase in inflammatory cells in the tumor microenvironment. Subsequently, tumor necrosis was demonstrated only in animals receiving the combination therapy, but not when each agent was applied as monotherapy. The results suggest that these synergistic treatment modalities may provide a novel and effective tool for future therapies of metastatic cancer.



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Expression of fusion proteins of the nicotinic acetylcholine receptor from mammalian muscle identifies the membrane-spanning regions in the alpha and delta subunits.

Chavez RA, Hall ZW.

Department of Physiology, University of California, San Francisco 94143-0444.

We have investigated the topology of the alpha and delta subunits of the nicotinic acetylcholine receptor (AChR) from mammalian muscle synthesized in an in vitro translation system supplemented with dog pancreatic microsomes. Fusion proteins were expressed in which a carboxy-terminal fragment of bovine prolactin was attached downstream of each of the major putative transmembrane domains, M1-M4 and MA, in the AChR subunits. The orientation of the prolactin domain relative to the microsomal membrane was then determined for each protein by a proteolysis protection assay. Since the prolactin domain contains no information which either directs or prevents its translocation, its transmembrane orientation depends solely on sequences within the AChR subunit portion of the fusion protein. When subunit-prolactin fusion proteins with the prolactin domain fused either M2 or M4 were tested, prolactin-immunoreactive peptides that were larger than the prolactin domain itself were recovered. No prolactin-immunoreactive peptides were recovered after proteolysis of fusion proteins containing prolactin fused after M1, M3, or MA. These results support a model of AChR subunit topology in which M1-M4, but not MA, are transmembrane domains and the carboxy terminus is extracellular.

PMID: 1730761 [PubMed - indexed for MEDLINE]

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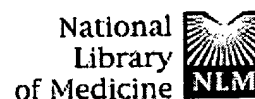
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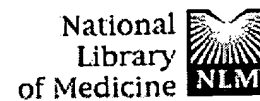
Induction of circulating and erythrocyte-bound IL-8 by IL-2 immunotherapy and suppression of its in vitro production by IL-1 receptor antagonist and soluble tumor necrosis factor receptor (p75) chimera.

Tilg H, Shapiro L, Atkins MB, Dinarello CA, Mier JW.

Division of Hematology-Oncology, New England Medical Center, Boston, MA.

The objective of this study was 1) to investigate the in vivo production of IL-8 in patients undergoing IL-2 immunotherapy and 2) to study the influence of IL-1Ra, soluble TNF receptor p75 (TNFRp75), and a TNFRp75-Fc fusion protein on IL-2-induced IL-8 production in vitro. Circulating IL-8 was assessed both in plasma and erythrocyte lysates prepared from patients undergoing IL-2 immunotherapy. IL-8 was detectable in the plasma within 2-4 h after the first IL-2 infusion, reached a peak level after 4 h, and declined rapidly to undetectable within 8 h. Erythrocyte-bound IL-8 was also detected within 4 h of the first IL-2 dose, but levels were higher than those measured in plasma and remained elevated long after the plasma levels had become undetectable. On day 4 of therapy, the increases in both plasma and the erythrocyte-lysate IL-8 levels induced by an IL-2 injection were less pronounced than on day 1. Although IL-1Ra and TNFRp75-Fc individually had only a modest suppressive effect on IL-2-induced IL-8 production by PBMC in vitro, the combination of IL-1Ra and TNFRp75-Fc markedly down-regulated IL-2-induced IL-8 synthesis and steady-state mRNA levels. TNFRp75 had no effect on IL-2-induced IL-8 synthesis. Our studies suggest that the transient detection of IL-8 in plasma early in the course of IL-2 treatment is due to erythrocyte sequestration and that suppressed synthesis, due in part to high levels of circulating IL-1 and TNF antagonists, may play a role later in the course of treatment.

PMID: 8397255 [PubMed - indexed for MEDLINE]



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Characterization of a fusion protein composed of the extracellular domain of c-kit and the Fc region of human IgG expressed in a baculovirus system.

Liu YC, Kawagishi M, Kameda R, Ohashi H.

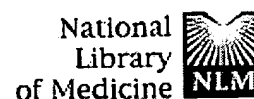
Pharmaceutical Research Laboratory, Kirin Brewery Co., LTD, Maebashi, Japan.

The extracellular domain of c-kit, which is the receptor for stem cell factor (SCF), was fused genetically to the Fc portion of human immunoglobulin G1. This chimeric protein, c-kitFc, was then expressed in the baculovirus system. The fusion product was secreted into the serum-free culture medium as a soluble dimeric form of approximately 210 Kda. The recombinant protein was easily purified by protein A affinity chromatography at approximately 25 micrograms protein per ml of medium. Binding assay and cross-linking assay showed that the fusion protein retained high affinity for binding SCF ($K_d = 0.3$ nM). Addition of the chimeric protein into the culture medium of SCF-dependent cells inhibited cell proliferation in a dose-dependent manner. These results suggest that the dimeric c-kitFc protein can be used as an antagonist of SCF for the study of hematopoietic progenitor cells.

PMID: 7506536 [PubMed - indexed for MEDLINE]

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(1):21-4

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Preclinical safety assessment of the recombinant TNF receptor-immunoglobulin fusion protein.

Winter M.

Pharmaceutical Research, Preclinical Toxicology, F. Hoffmann-LaRoche Ltd., Basel, Switzerland.

The tumor necrosis factor (TNF) is now recognized as one of the most pleiotropic mediators of host defense, immune regulation, and inflammatory response. Due to its broad spectrum of effects, TNF has been implicated as a key mediator in the pathogenesis of acute and chronic inflammatory conditions. The inhibition of bioactive TNF could therefore provide a substantial therapeutic benefit. One approach to a potent TNF antagonist is to use recombinant protein technology in the design of a molecule in which the heavy-chain sequences of an immunoglobulin are fused with the ligand-binding region of the TNF receptor. This paper describes some aspects of the preclinical safety evaluation of the recombinant human TNF receptor-immunoglobulin fusion protein (TENEFUSE). Specific emphasis was placed on transgenic and gene-deleted mice models as central sources of information in the safety evaluation of this TNF antagonist.

PMID: 9073530 [PubMed - indexed for MEDLINE]

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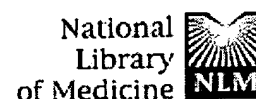
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Treatment with the interleukin-1 receptor antagonist and soluble tumor necrosis factor receptor Fc fusion protein does not prevent endotoxin-induced preterm parturition in mice.

Fidel PL Jr, Romero R, Cutright J, Wolf N, Gomez R, Araneda H, Ramirez M, Yoon BH.

Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, Michigan, USA.

OBJECTIVE: To determine whether the administration of anticytokine agents, the interleukin-1 receptor antagonist (IL-1ra) and a soluble tumor necrosis factor receptor Fc fusion protein (sTNFR-Fc), prevents endotoxin-induced preterm delivery in mice. **METHODS:** C3H/HeN pregnant mice at 15 days of gestation (70% gestation) were randomized to receive phosphate-buffered saline (PBS) or lipopolysaccharide (LPS) (50 micrograms/mouse) intraperitoneally (i.p.). Randomly selected PBS- or LPS-treated mice were additionally treated intravenously (i.v.), i.p., or subcutaneously (s.c.) every 3 hours with IL-1ra (1-50 mg) or every 12 hours with sTNFR-Fc (200-400 micrograms) beginning 1 hour before LPS injection. Animals were observed for vaginal bleeding and preterm delivery. **RESULTS:** Mice treated i.p. with 50 micrograms LPS (n = 13) had a shorter injection-to-delivery interval than mice treated similarly with PBS (n = 19) (median 13.5 hours, range 10-105 versus median 86.8 hours, range 53-120, respectively; P < .001). Saline-treated mice given 10 mg IL-1ra every 3 hours i.p. (n = 3) or 200 micrograms sTNFR-Fc every 12 hours i.v. (n = 4) had similar injection-to-delivery intervals as PBS-treated control mice (median 70 hours, range 70-76 versus median 58 hours, range 50-120, respectively). Similarly, LPS-treated mice given PBS every 3 hours (n = 20) had injection-to-delivery intervals comparable to LPS-treated mice (n = 13) (median 15.5 hours, range 9.8-92 versus median 13.5 hours, range 10-105, respectively). Lipopolysaccharide-treated mice given i.p. injections of 1 (n = 4), 10 (n = 31), or 50 (n = 15) mg of IL-1ra every 3 hours did not have longer injection-to-delivery intervals compared with LPS-treated mice (n = 13) (medians 11.6, 15, 14.5 and 13.5 hours; ranges 10.8-12, 8-95, 11-92, and 10-105, respectively). Lipopolysaccharide-treated mice given i.v. injections of 200

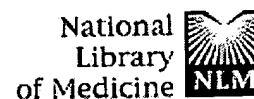
(n = 4) or 400 (n = 9) micrograms sTNFR-Fc every 12 hours did not have longer injection-to-delivery intervals compared with LPS-treated mice (n = 8) (medians 23.3, 22.5, and 21.9 hours; ranges 14.8-33, 15-95.5, and 15.5-44, respectively). The median injection-to-delivery interval of LPS-treated mice given both IL-1ra (10 mg) every 3 hours i.p. and sTNFR-Fc (200 micrograms) every 12 hours i.v. (n = 5) was not different from that of LPS-treated mice (median 26 hours, range 24.5-72 versus median 13.5 hours, range 10-105, respectively; $P > .05$). CONCLUSION: The anticytokine agents IL-1ra and sTNFR-Fc did not prevent preterm delivery or prolong pregnancy in endotoxin-induced preterm labor in mice.

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(4):309-15

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Interferon-gamma receptor extracellular domain-IgG fusion protein produced in Chinese hamster ovary cells as mixture of glycoforms.

Mesa C, Dembic Z, Garotta G, Fountoulakis M.

F. Hoffmann-La Roche, Ltd., Basel, Switzerland.

Glycosylation of proteins fulfills important functions and because of its diversity contributes to apparent protein heterogeneity. We investigated the heterogeneity of a fusion protein comprising the extracellular domain of the human interferon-gamma (IFN-gamma) receptor and parts of the human IgG3 constant region, a potential IFN-gamma antagonist. The protein was produced in Chinese hamster ovary (CHO) cells and was secreted into the culture medium as an 175 kD glycoprotein. Glycosylation represented approximately one-third of the apparent molecular mass of the fusion protein, consisted of N- and O-linked carbohydrate moieties, and included sialic acid residues as part of both N- and O-linked oligosaccharides. Fusion protein forms with different apparent molecular masses and charges were separated by ion-exchange chromatography. Preparative electrofocusing revealed a wide spectrum of glycoforms. Glycosylation of the fusion protein and of soluble IFN-gamma receptors, comprising the extracellular domain of the native sequence, expressed in insect and CHO cells did not interfere with affinity of ligand binding.

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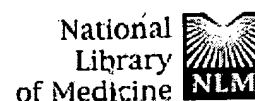
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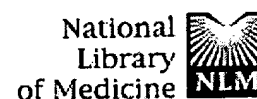
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Phase I trial of interleukin 2 in combination with the soluble tumor necrosis factor receptor p75 IgG chimera.

Trehu EG, Mier JW, Dubois JS, Sorce D, Klempner MS, Epstein M, Dinarello CA, Shapiro L, Kappler K, Ronayne L, Atkins MB.

Divisions of Hematology-Oncology and Infectious Diseases, Tufts University School of Medicine and New England Medical Center Hospitals, Boston, Massachusetts 02111, USA.

Our purpose was to determine the effective biological dose and/or maximum tolerated dose of recombinant human tumor necrosis factor receptor:IgG chimera (rhuTNFR:Fc; Immunex, Seattle, WA) in combination with interleukin 2 (IL-2) with regard to reduction in IL-2 toxicity and modulation of biological effects of high-dose IL-2 administration. Twenty-four patients with metastatic cancer were treated with escalating doses of rhuTNFR:Fc at 1, 1, 5, 10, and 20 mg/m² i.v. on days 1 and 15 (dose levels 1-5) or 10, 20, and 30 mg/m² days 1 and 15 plus 50% dose on days 3, 5, 17, and 19 (dose levels 6-8) prior to IL-2 at doses of 300,000 IU/kg (dose level 1) and 600,000 IU/kg (dose levels 2-8) i.v. every 8 h on days 1-5 and 15-19. The t_{1/2} of rhuTNFR in patients receiving IL-2 was 72 h. The median number of IL-2 doses was 24, and central nervous system, skin, and cardiac arrhythmias were the major dose-limiting toxicities. TNF bioactivity was inhibited, and the polymorphonuclear leukocyte chemotactic defect normally seen with IL-2 was not observed. Increases in C-reactive protein, IL-6, IL-8, and IL-1 receptor antagonist levels were partially suppressed relative to historical controls, whereas peripheral blood mononuclear cell phenotypes, urinary nitrate, endothelial adhesion molecule expression in skin biopsies, and cellular infiltrates in tumor biopsies were consistent with findings in patients treated with IL-2 alone. Four patients developed thyroid dysfunction. There were five responses: two complete responses (both melanoma) and three partial responses (response rate, 21%). rhuTNFR:Fc may modulate the toxicity and some of the biological effects of IL-2 while preserving antitumor activity. Dose level 6 (10 mg/m² on days 1 and 15, and 5 mg/m² on days 3, 5, 17, and 19) has been chosen for a randomized, double-blind, placebo-controlled trial of IL-2 with and without rhuTNFR:Fc.



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Combination benefit of treatment with the cytokine inhibitors interleukin-1 receptor antagonist and PEGylated soluble tumor necrosis factor receptor type I in animal models of rheumatoid arthritis.

Bendele AM, Chlipala ES, Scherrer J, Frazier J, Sennello G, Rich WJ, Edwards CK 3rd.

Amgen Colorado, Boulder, USA.

OBJECTIVE: To determine the potential for additive or synergistic effects of combination therapy with the recombinant anticytokine agents interleukin-1 receptor antagonist (IL-1Ra) and PEGylated soluble tumor necrosis factor receptor type I (PEG sTNFRI) in established type H collagen-induced arthritis (CIA) and developing adjuvant-induced arthritis (AIA) in rats. **METHODS:** Rats with established CIA or developing AIA were treated with various doses of IL-1Ra in a slow-release hyaluronic acid vehicle or with PEG sTNFRI, either alone or in combination with the IL-1Ra. The effects of treatment were monitored by sequential caliper measurements of the ankle joints or hind paw volumes, final paw weights, and histologic evaluation with particular emphasis on bone and cartilage lesions. **RESULTS:** Combination therapy with IL-1Ra and PEG sTNFRI in rats with CIA resulted in an additive effect on clinical and histologic parameters when moderately to highly efficacious doses of each protein were administered. Greater-than-additive effects were seen when an inactive dose of IL-1Ra was given in combination with moderately to minimally active doses of PEG sTNFRI. Plasma levels associated with the latter effect (for both proteins) were similar to those seen in rheumatoid arthritis (RA) patients in clinical trials with these agents. Combination therapy in the AIA model generally resulted in additive effects, but some parameters showed a greater-than-additive benefit. **CONCLUSION:** The results provide preclinical support for the hypothesis that IL-1Ra administered in combination with PEG sTNFRI might provide substantially more clinical benefit to RA patients than either agent alone at blood levels that are currently achievable in patients.

Yaen, Christopher

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